Biology of the Stress Response

Raymond P. Stowe, Ph.D.
Department of Pathology

Psychoneuroimmunology

The study of the link between psychological states and the functioning of the immune system

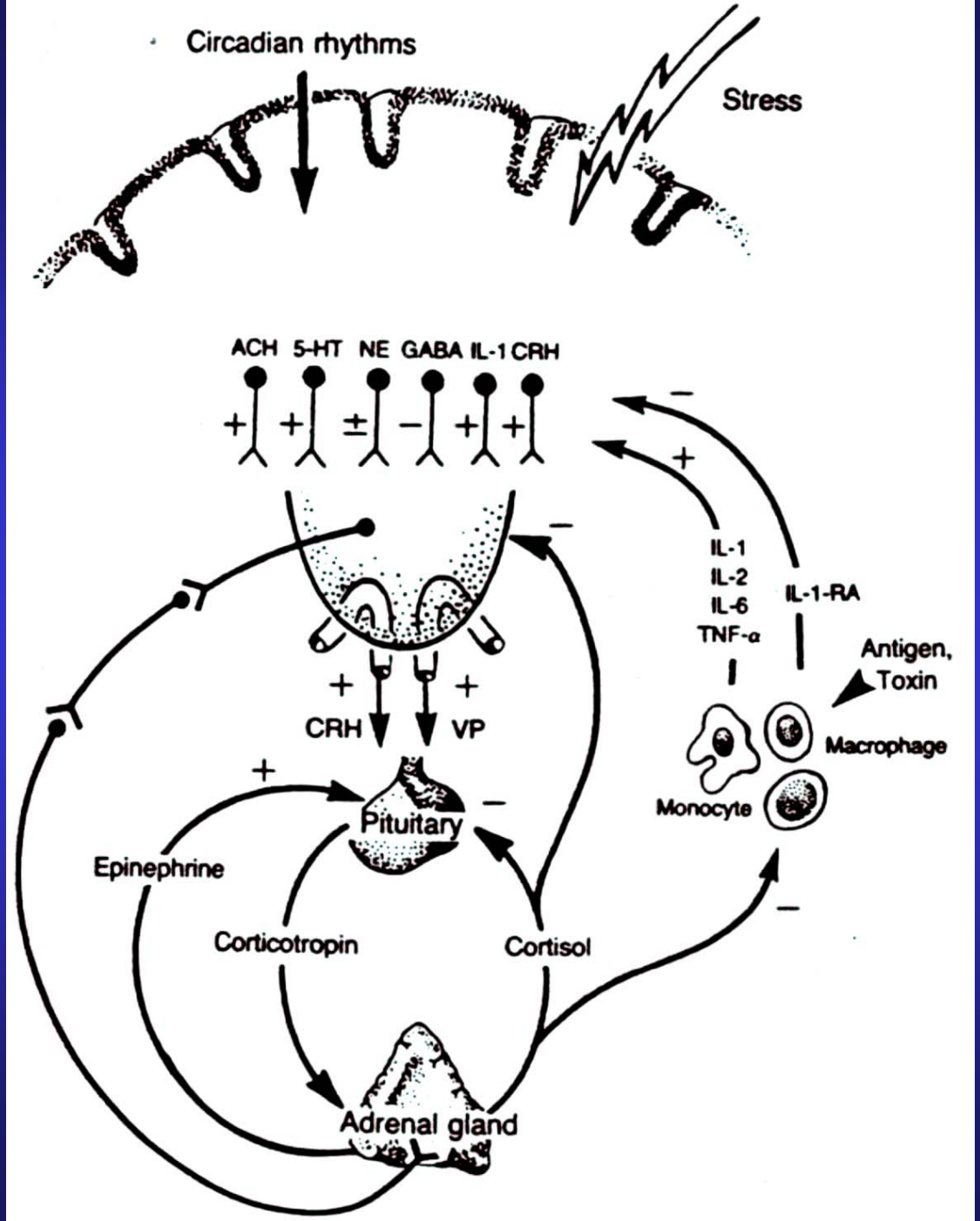
The link between the two is provided by the Central Nervous System (CNS)

Our psychology affects our nervous system which in turn affects our immunity

Alteration of the function of the immune system is mediated by hormones whose plasma concentration is regulated by the central nervous system

Hypothalamus-pituitary-adrenal (HPA)
Sympathetic nervous system (SAM)

CNS activity modulates the concentration of plasma hormones



The endocrine response to stress is extremely complex and involves a number of feedback mechanisms

Stress-induced hormonal alterations have been associated with *Clinical effects* such as:

- An increased susceptibility to viral infections
- Activation of latent viral infections
- Onset and exacerbation of autoimmune diseases
- Progression of atherosclerotic heart disease and myocardial infarctions
- Stroke
- Depression

Studies of Stress and Immune Function

Human Studies of Stress

Laboratory studies

- Volunteers are exposed to acute, short-term stressors (e.g. making speeches)
- Immune functioning is simultaneously measured

Shows that it takes as little as five minutes for a stressor to inhibit the ability of the immune system to respond effectively

Also exposure to antigens; record illness occurrences

Antigen Exposure

Cohen *et al*. (1999), Psychological stress, cytokine production, and severity of upper respiratory illness. Psychosom. Med. 61:175-80.

-55 subjects were infected with influenza A virus
-the Perceived Stress Scale (PSS) was used to assess the degree of stress (High vs. Low)

Measures included: self-reported respiratory symptoms
IL-6 concentrations in nasal secretions

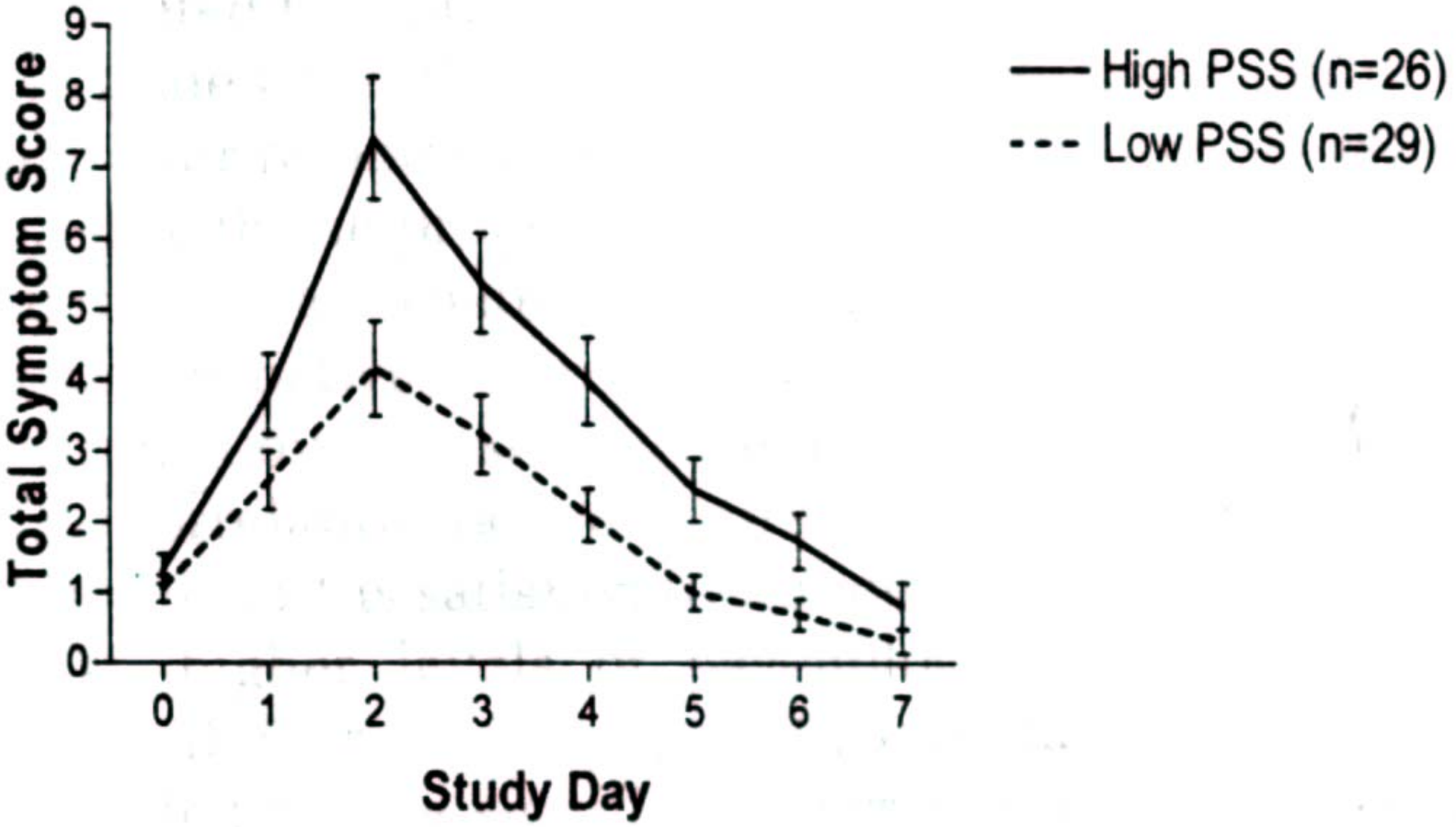


Fig. 1. The association between psychological stress (low = below median and high = above median) and symptoms of upper respiratory illness among subjects infected with an influenza A virus. Viral inoculation occurred at the end of day 0. SEs are indicated.

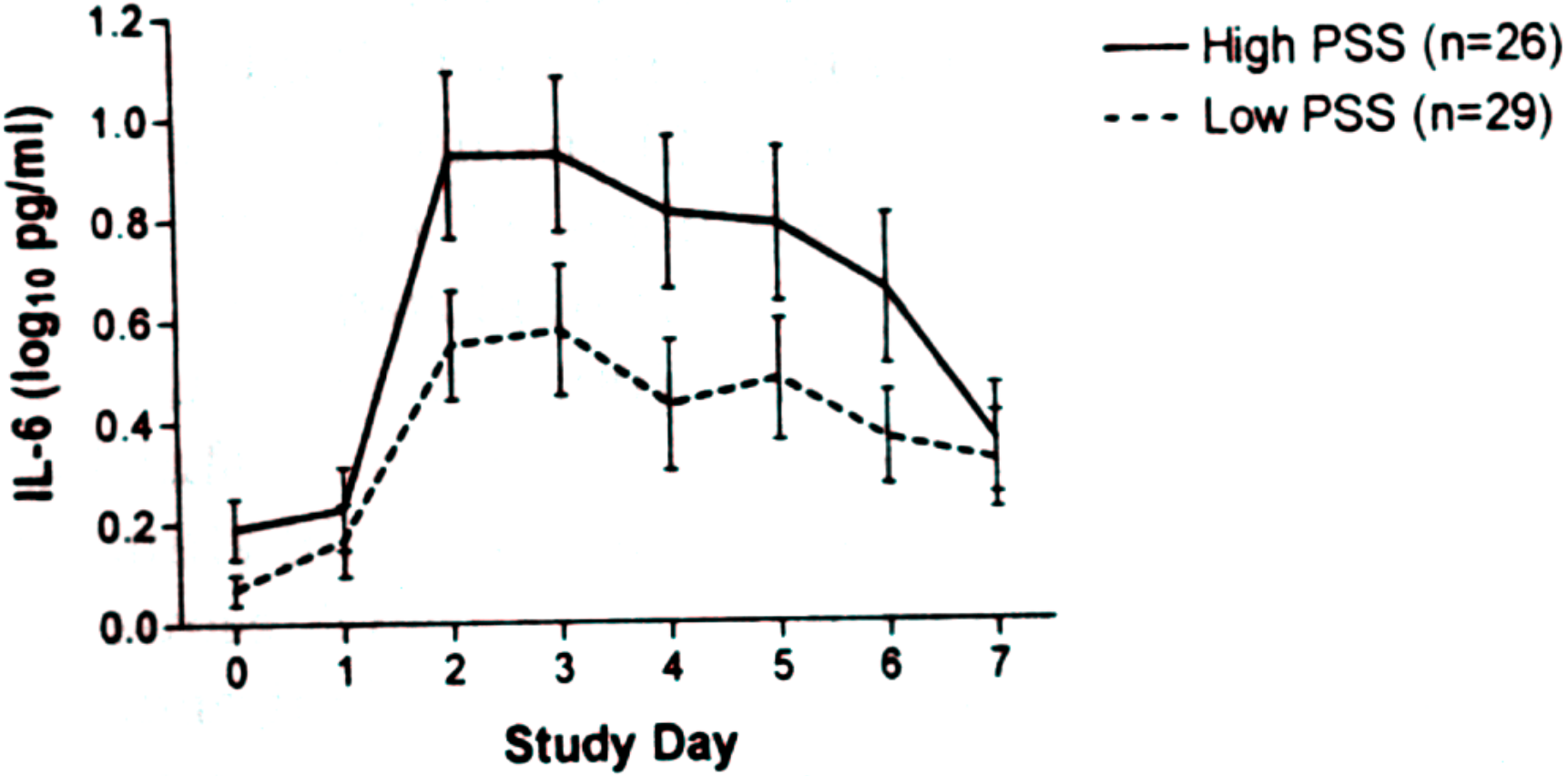


Fig. 3. The association between psychological stress (low = below median and high = above median) and IL-6 in nasal secretions among subjects infected with an influenza A virus. Viral inoculation occurred at the end of day 0. SEs are indicated.

Conclusion - Cohen *et al.* (1999)

•Psychological stress predicted a greater expression of illness and an increased production of IL-6 in response to an upper respiratory infection

First study to provide evidence that psychological stress can influence infectious illness through biological pathways

Studies of Stress and Immune Function

Longitudinal or field studies

- Involves following-up individuals who have suffered significant stresses at one point over long period of time after the stressful event or time period

Shows that strong stresses lead to significantly more illness over time

This effect remains after controlling for factors that may account for increased illness such as smoking and substance abuse

Also shows that the immune system can remain suppressed in the long term

Ohio State University
Studies by Ronald Glaser and group

Stress-associated immune modulation

Immune changes associated with academic stress and caregivers:

- Decreased NK cell activity
- Decreased proliferative responses of lymphocytes
- Decreased production of IFN-γ by lymphocytes
- Decreased IL-2 receptor expression

Question: As these temporary changes, or can these changes lead to increased susceptibility to viral infections (i.e., herpesviruses)

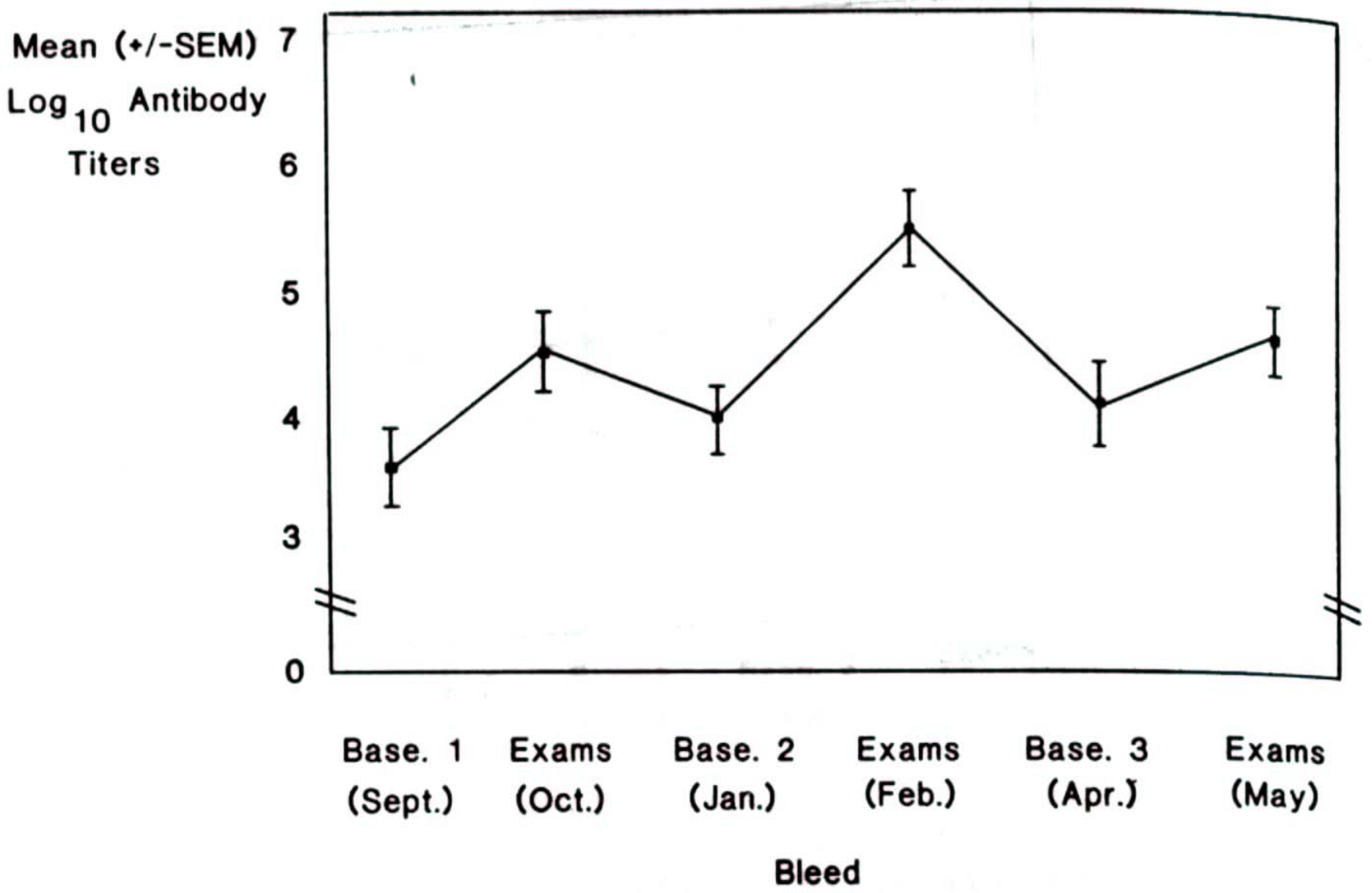


FIG. 1. Antibody titer to the EBV VCA complex of proteins (IgG) across three baseline and three examination blood samples. Antibody titers were determined using the indirect IF test as previously described (Glaser et al., 1987).

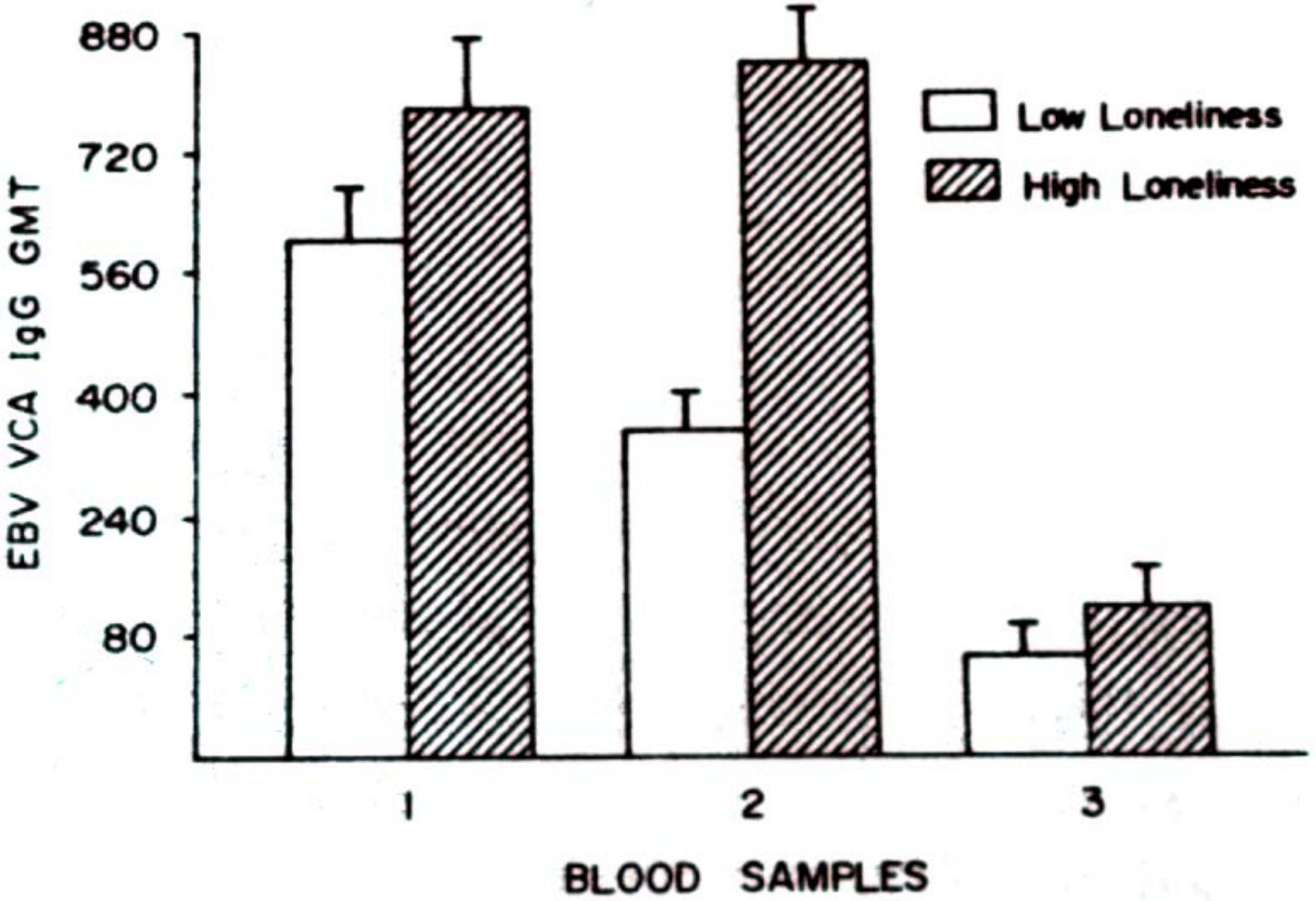


Fig. 1. Changes in the GMT (± SE) of EBV VCA IgG in high- and low-loneliness medical students across the three sample points.

Conclusion - Glaser *et al.* (1985-)

- Review of studies indicate that stress can have a significant impact on immune function, ranging from down-regulation of T-cell responses to decreases in cytokine production

- These changes are associated with reactivation of latent herpesviruses, decreased antibody response to viral vaccines, increased risks of colds, and delays in wound healing

Role of HPA and IL-6 in stress-induced Reactivation of Latent HSV

Noisakran *et al.*, J. Immunol., 1998

Investigated hypothermic stress and reactivation of HSV-1 in mice:

-Does hypothermic stress induce HSV-1 reactivation
-Is viral reactivation mediated by the HPA axis

Treatment of hypothermic mice with the glucocorticoid synthesis inhibitor cyanoketone (CK)

Table III. *CK blocks stress-induced reactivation of HSV-1*[a]

Treatment	Hyperthermic Stress	Corticosterone (ng/ml)	HSV-1 Reactivation
Vehicle	No	61 ± 15[b]**	0/8 (0%)
Vehicle	Yes	798 ± 38	6/21 (29%)
CK (50 mg/kg)	Yes	429 ± 25**	3/14 (21%)
CK (75 mg/kg)	Yes	250 ± 20**	1/7 14%)
CK (100 mg/kg)	Yes	70 ± 56**	0/6 (0%)
Dexamethasone (1.0 mg/ml)	No	22 ± 2**	0/8 (%)
Dexamethasone (1.0 mg/ml)	Yes	283 ± 168*	1/9 (11%)

[a] Mice latently infected with HSV-1 were given vehicle, dexamethasone, or CK at the indicated concentration as described (see *Materials and Methods*). Mice were or were not exposed to hyperthermic stress, and blood was obtained 1 h following the stressor to determine corticosterone levels. The mice were subsequently killed 24 h poststress, and the TGs were removed and assessed for viral reactivation (i.e., the recovery of infectious virus). CK alone was not found to induce reactivation ($n = 5$ for 50 mg/kg and 100 mg/kg; not tested for 75 mg/kg).

[b] Numbers are mean ± SEM.

**$p < 0.01$, *$p < 0.05$ comparing vehicle, hyperthermic stress group with all other groups as determined by ANOVA and Tukey's t test.

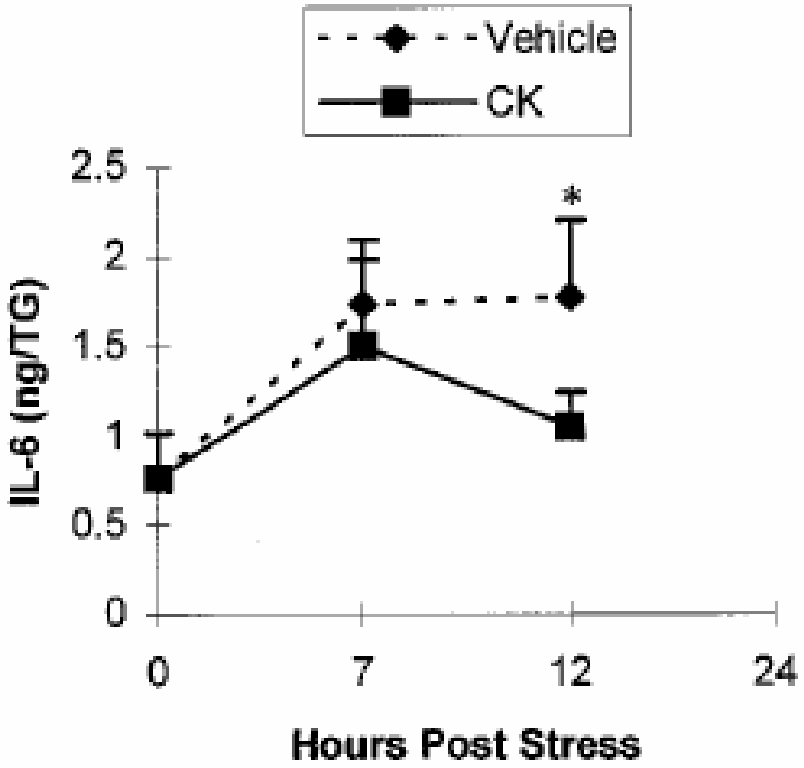


FIGURE 5. CK partially blocks IL-6 protein in the TG of hyperthermically stressed, mice latently infected with HSV-1. CK (100 mg/kg) or vehicle was administered to mice latently infected with HSV-1 24 and 2 h before hyperthermic stress. At 7 and 12 h poststress, the mice ($n = 4$/time point/group) were killed, and the TG was removed and processed as previously described (25). Supernatants from homogenized TGs were assayed for IL-6 by ELISA as described (25). *$p < 0.05$ comparing the stressed, vehicle-treated group with the nonstressed control. Bars represent SEM.

Conclusion - Noisakran *et al*., J. Immunol., 1998

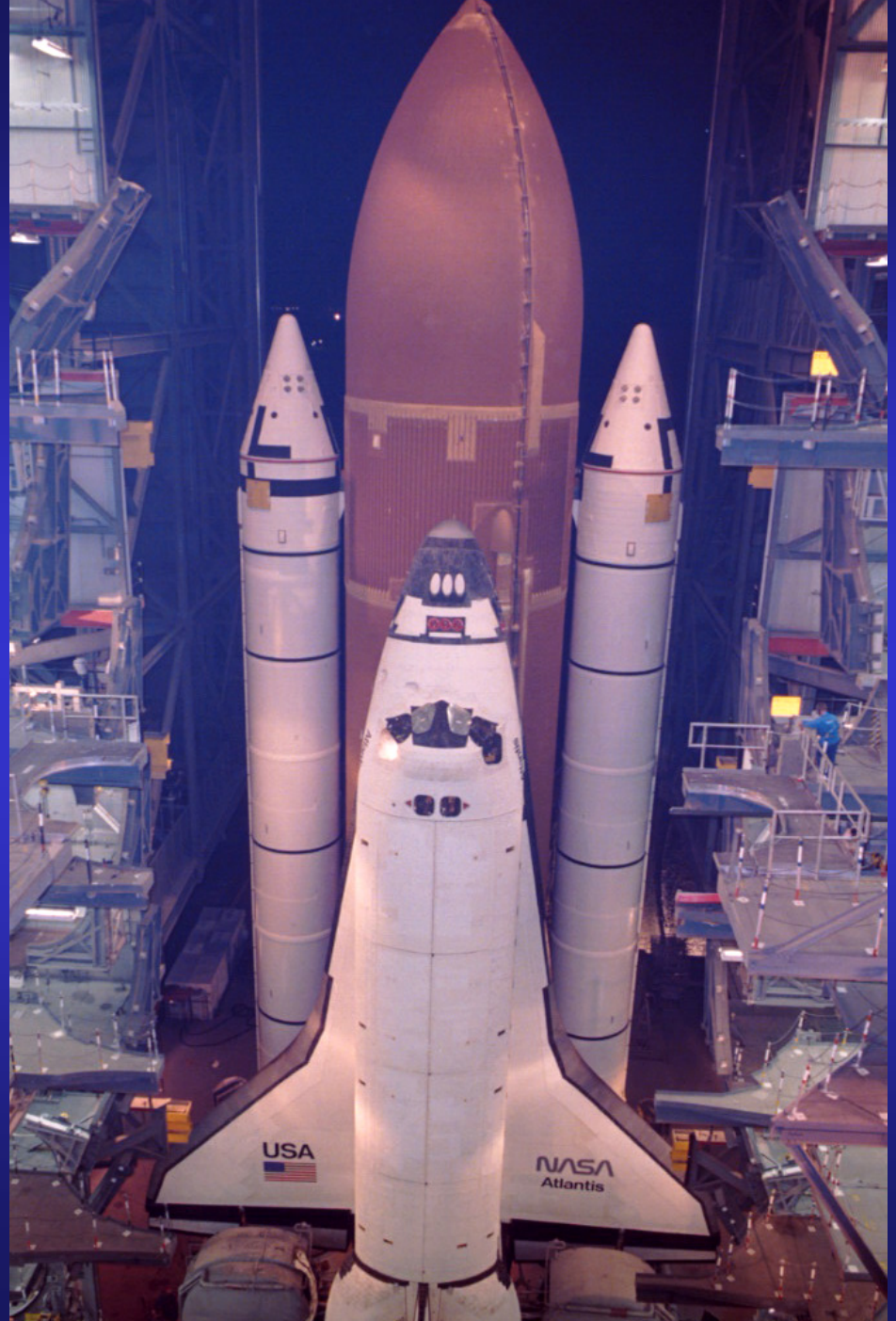
- Preadministration of CK blocked stress-induced elevation of corticosterone in a dose-dependant manner
- Inhibition of corticosterone synthesis correlated with reduced levels of HSV-1 reactivation
- CK blocked the stress-induced rise in IL-6 mRNA and protein expression

Increasing interest in IL-6

Increased levels are associated with aging and chronic stress (Kiecolt-Glaser *et al.*, PNAS 100:9090-5, 2003)

Linked to cardiovascular disease due to the central role this cytokine plays in the production of C-reactive protein (CRP) , an important risk factor for myocardial infarction (Pradhan *et al.*, JAMA 286:327-34, 2001)

IL-6 and CRP also play a pathogenic role in a number of diseases (osteoporosis, arthritis, congestive heart failure, etc.)


USA
NASA
Atlantis

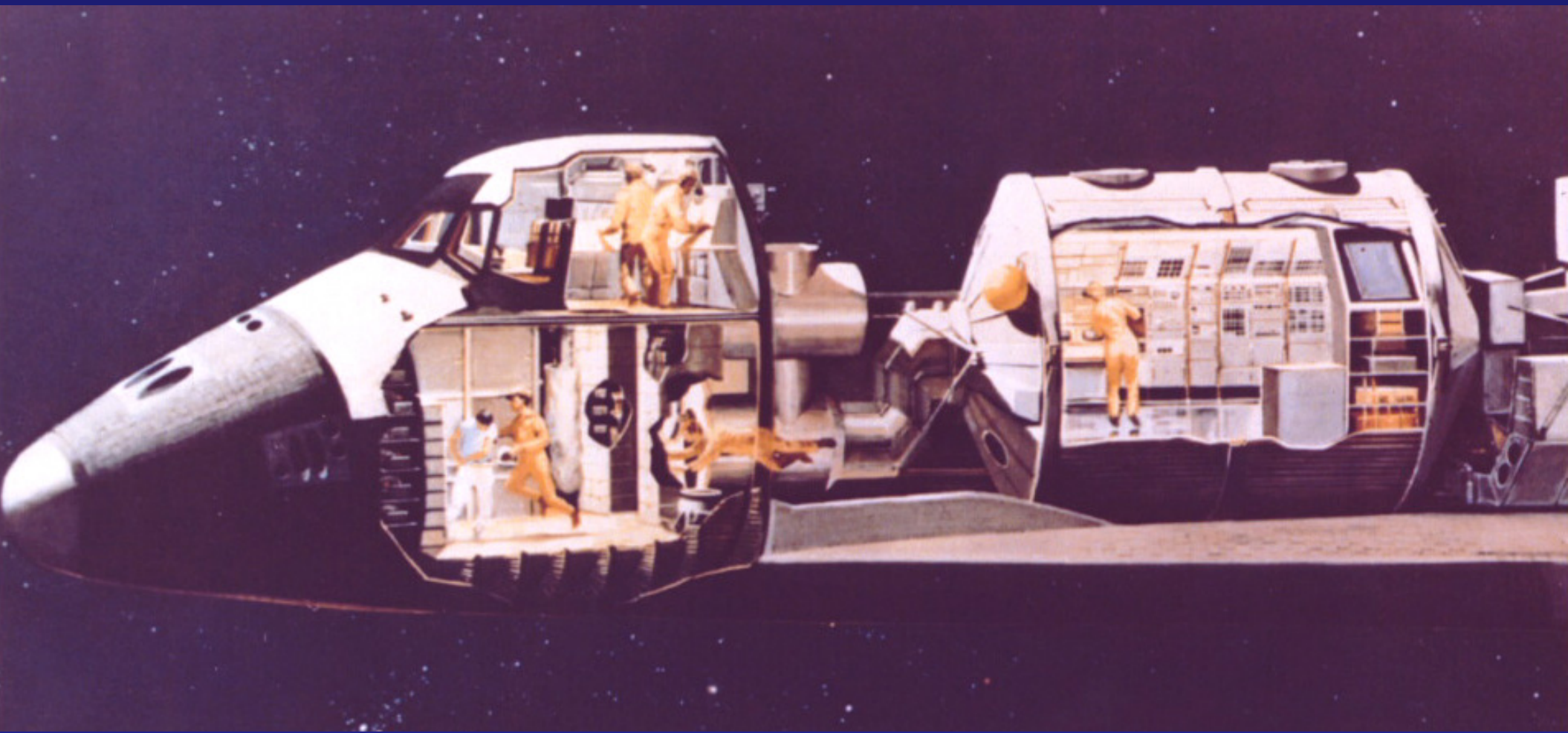
U.S. and Russian Immunology Studies

- Reduced lymphocyte mitogenic response
- Altered leukocyte subpopulations (PMNs, band neutrophils, NK cell # and function)
- Decreased DTH responses during spaceflight

Stress (physical and psychological) may be a factor in the reduced immune responses of astronauts

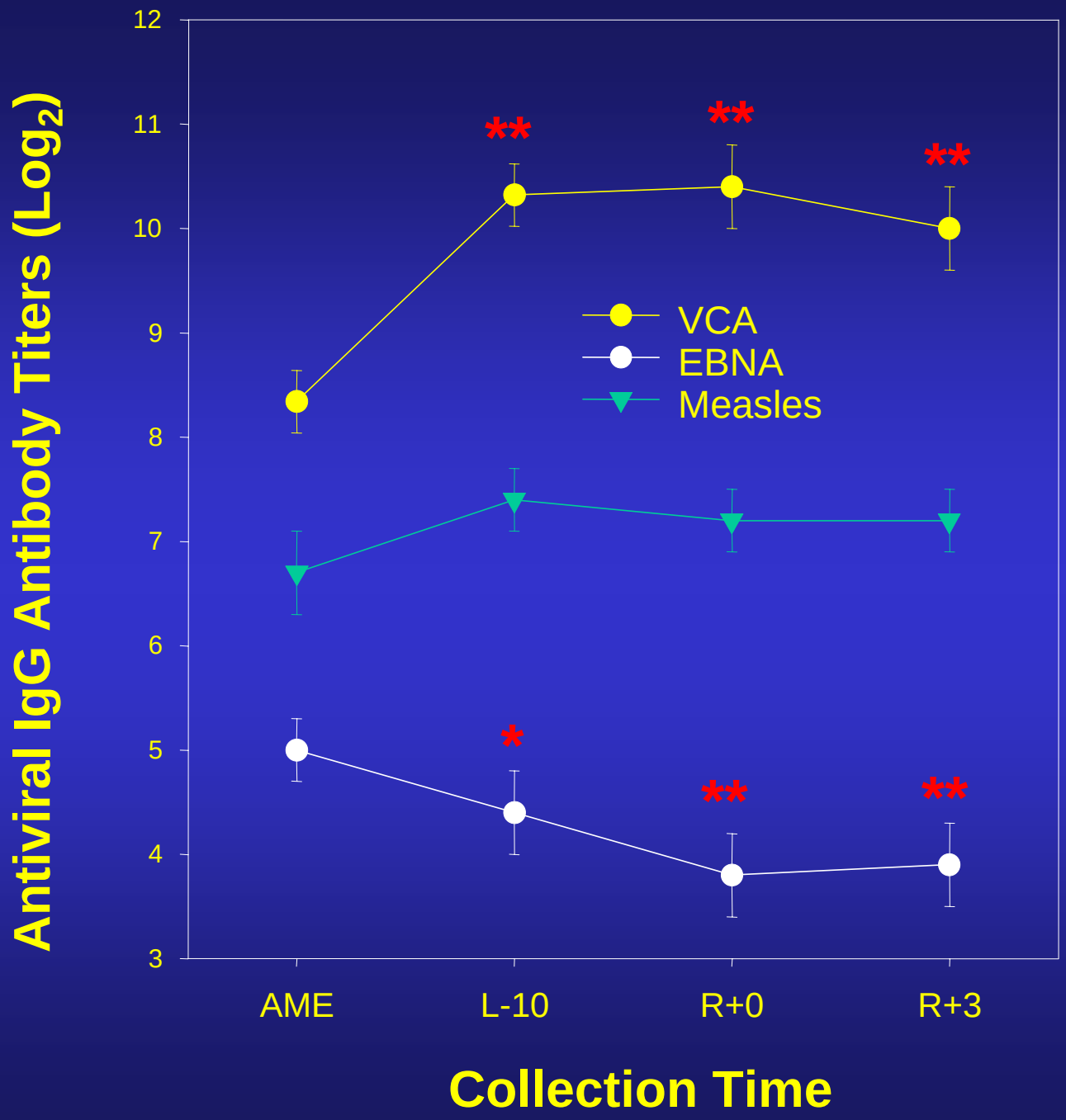
Space Flight Factors Increasing Infectious Disease Risk

- Changes in immune response
- Closed environment/crowded living & working conditions
- Inability to isolate contagious crew member
- Limited in-flight diagnostics and treatment capabilities
- Limited clean-up and disinfecting capability
- Increased radiation exposure



Latent Viruses

- Herpesviruses, such as Epstein-Barr virus (EBV), are widespread among humans (>90%)
- Not mitigated by a pre-flight quarantine period
- Subject to intermittent reactivation
- May result in clinical symptoms/disease


Antiviral IgG Antibody Titers (Log2)
12
11
10
9
8
7
6
5
4
3
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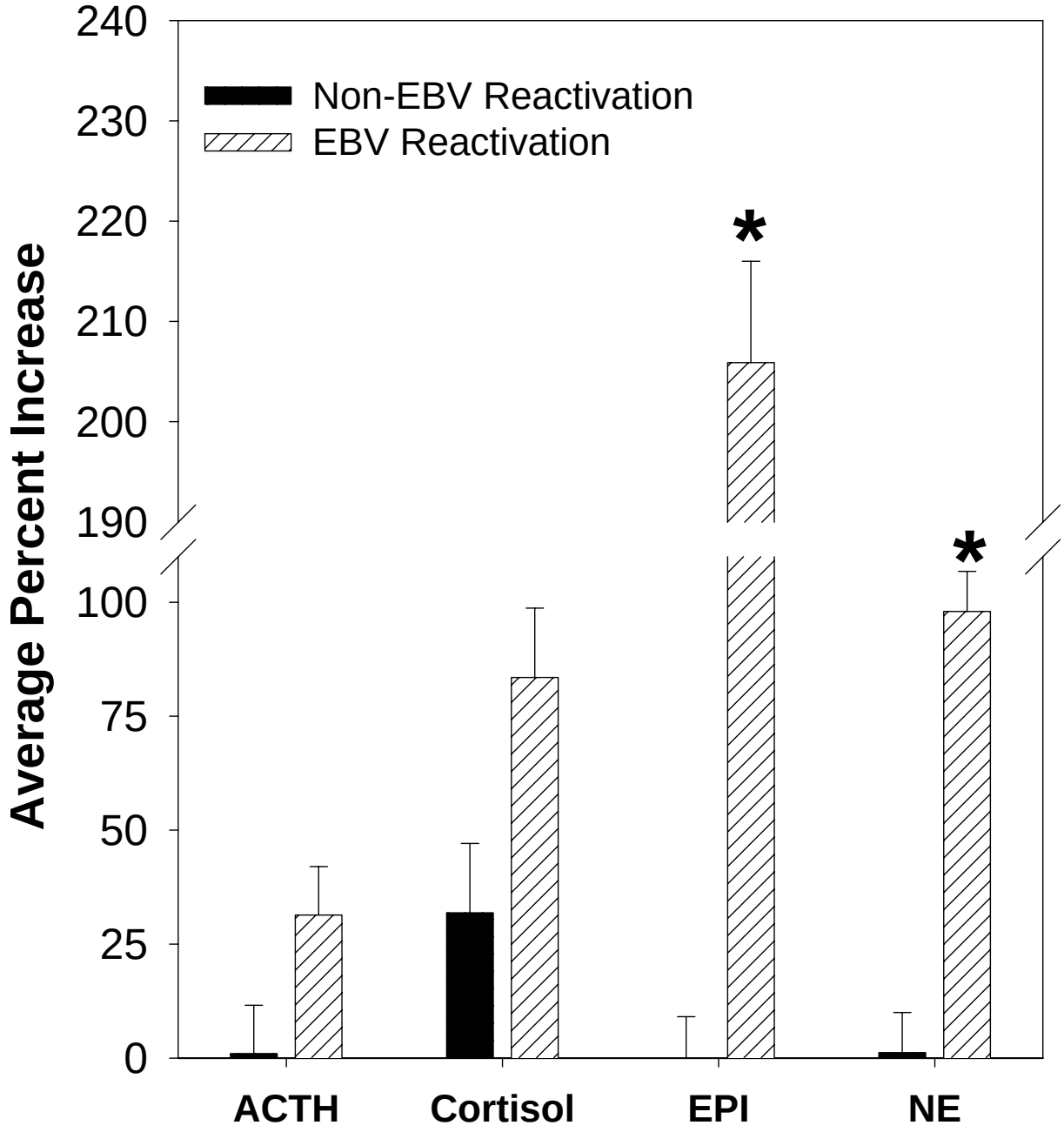
VCA
EBNA
Measles
AME
L-10
R+0
R+3
Collection Time


Non-EBV Reactivation
EBV Reactivation
Average Percent Increase
240
230
220
210
200
190
100
75
50
25
0
*
*
ACTH
Cortisol
EPI
NE

MS3

CMV

L-60 L-30 L-10 FD2 FD5 R+0 R+3 R+5 R+15

Inflight

Postflight

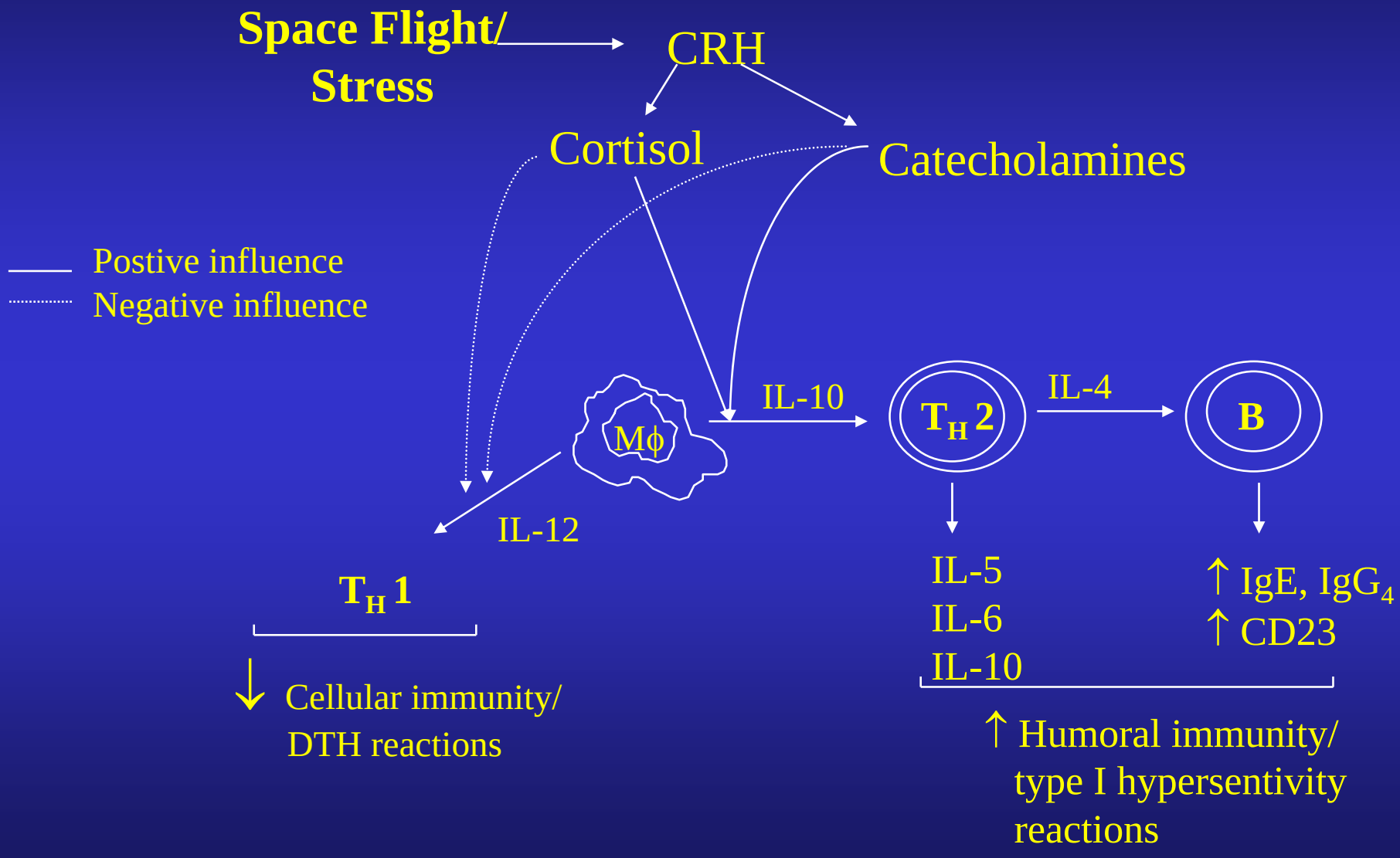
Preflight

Cortisol (ug/dL)

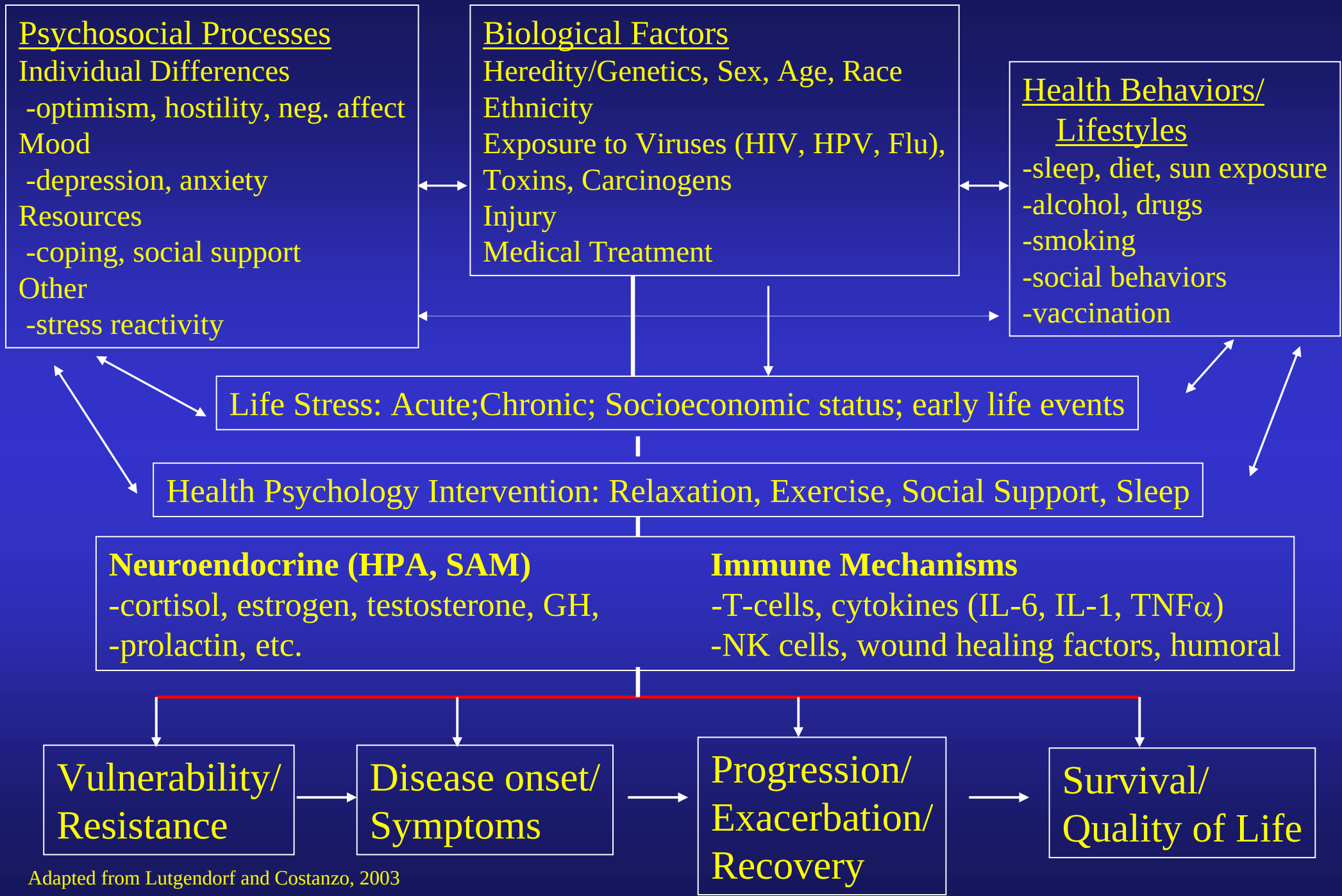
25
20
15
10
5

L-28 L-27 FD2 FD4 FD6 FD8 R+0 R+3 R+6 R+7 R+15 R+16

Proposed Model for Stress-Induced Decreases In Cellular Immunity



Adapted from Elenkov *et al.*, Proc. Assoc. Am. Physicians, 1996



Adapted from Lutgendorf and Costanzo, 2003